UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: September 24, 2020

SUBJECT: **Paraquat**: Response to Comments on the Draft Human Health Risk Assessment

PC Code: 061601
Decision No.: 559059
Petition No.: NA
Risk Assessment Type: Response to Comments
TXR No.: NA
MRID No.: NA

DP Barcode: D456000
Registration No.: NA
Regulatory Action: Registration Review
Case No.: 0262
CAS No.: 1910-42-5
40 CFR: § 180.205

FROM: Wade Britton, MPH, Environmental Health Scientist
Thurston Morton, Chemist
Austin Wray, Ph.D., Toxicologist
Risk Assessment Branch 4 (RAB4)
Health Effects Division (HED; 7509P)

AND

Aaron Niman, Environmental Health Scientist
Toxicology and Epidemiology Branch (TEB)
HED (7509P)

THROUGH: Shalu Shelat, Branch Chief
RAB4/HED (7509P)

AND

David J. Miller, Acting Branch Chief
TEB/HED (7509P)

TO: Ana Pinto, Chemical Review Manager
Marianne Mannix, Team Leader
Kelly Sherman, Branch Chief
Risk Management and Implementation Branch III (RMIB III)
Pesticide Re-evaluation Division (PRD; 7508P)

Paraquat dichloride is a restricted-use quaternary ammonium herbicide employed for weed control and as a harvest aid in the United States. It is currently undergoing Registration Review at the Office of Pesticide Programs (OPP). The draft human health risk assessment (HHRA) and ecological risk assessment authored by the Health Effects Division (HED) and Environmental Fate and Effects Division (EFED), respectively, were published on October 16, 2019 and open for public comment through December 16, 2019. Numerous comments were received from a wide range of stakeholders including environmental non-government organizations (e.g. Beyond Pesticides, Environmental Working Group, Center for Biological Diversity), public interest advocacy groups (e.g. California Rural Legal Assistance Foundation, United Parkinson's Advocacy Council), pesticide registrants (e.g. Syngenta), government agencies (e.g. Washington State Department of Agriculture, United States Department of Agriculture), and individual members of the general public. Comments from the non-government organizations and advocacy groups were also co-signed by affiliated organizations. This memo contains the agency's responses to public comments submitted during the comment period that were directed at the HHRA (Britton W. *et al.,* D430827, 2019). The public comments and agency responses are organized based on the sections of the HHRA to which they pertain and then by content of the comment. Public comments submitted from multiple sources that were similar in substance were binned together and a single response was provided. For topics that had lengthy public comments (e.g. the Parkinson's disease systematic review), the public comments were summarized in the agency's response rather than reprinting each comment in its entirety. The public comments were otherwise reprinted in italics and followed by the agency response below. The agency thanks all commenters for their submissions.

I. Parkinson's Disease Systematic Review

General Comments on the Methods and Conclusions of the Parkinson's Disease Systematic Review (Beyond Pesticides, California Rural Legal Assistance Foundation, Center for Biological Diversity, Pesticide Action Network and the United Parkinson's Disease Advocacy Council, Syngenta)

EPA Response: The agency received numerous comments on its Parkinson's disease (PD) systematic review conducted as part of the paraquat registration review. Those that disagreed with the agency's conclusions, including Beyond Pesticides, California Rural Legal Assistance Foundation, Center for Biological Diversity, Pesticide Action Network and the United Parkinson's Disease Advocacy Council, pointed to positive associations in epidemiology studies and supporting laboratory animal and mechanistic data from the open literature as evidence that there is an association between paraquat exposure and PD. On the other end of the spectrum, Syngenta Crop Protection LLC (hereafter referred to as Syngenta), a registrant of paraquat dichloride, agreed with the overall conclusions of the systematic review, but found some disagreement with HED's characterization of individual study quality and interpretation of the results. Comments from both perspectives cited studies that were considered by the agency in its systematic review, as well as additional publications that were either excluded based on the inclusion criteria, were not captured in the search strategy, or were published after the open literature search. After consideration of the critiques and perspectives from the commenters and review of the newly identified publications, the agency remains confident in its review process and its conclusion that the weight of evidence was insufficient to link paraquat exposure from pesticidal use of US registered products to PD in humans.

The agency arrived at its conclusion after a thorough, systematic review of publications from the open literature and data submitted to the agency voluntarily or as a requirement of registration. The agency collaborated with the National Toxicology Program (NTP) to develop a search strategy for systematically

screening the open literature for human, animal, and *in vitro* publications that investigated the relationship between paraquat exposure and effects associated with PD. In total, 7,166 publications were screened as part of this collaboration. In addition, the agency conducted a separate systematic review of the epidemiology literature that investigated the relationship between paraquat exposure and any adverse human health outcome. A total of 576 publications were screened in this general epidemiology systematic review. Between these two systematic reviews and unpublished studies in the paraquat toxicity database, the agency compiled a PD literature database for the systematic review of 28, 217, and 244 human, animal, and *in vitro* studies, respectively, that were relevant to evaluating the association between paraquat exposure and PD. Most of the studies referenced in the public comments were included in this literature database.

Each study in the PD literature database was individually evaluated for quality, substance, and environmental relevance. Environmental relevance was defined as the likelihood that a given effect would result from an exposure scenario anticipated to occur from typical use of registered paraquat products (e.g. oral including dietary, dermal, and inhalation exposure). The agency integrated environmental relevance considerations into the systematic review in order to contextualize hazard information in terms of risk. This was an important consideration, particularly for the animal literature, given that many of the paraquat studies investigating PD-like hallmarks used a route of administration (e.g. intraperitoneal, intracranial, intravenous, etc.) that did not reflect an anticipated exposure scenario (oral, dermal, and inhalation) for registered pesticidal uses of paraquat. Moreover, the agency determined that, based on available data, toxicokinetic differences between injection and the anticipated routes of administration for paraquat precluded using data from injection studies for evaluating risk from pesticidal uses. These studies are, therefore, not relevant to establishing a causative relationship between exposure from pesticidal uses of paraquat and PD.

The quality assessment for open literature studies was conducted in accordance with the OPP Epidemiology Framework[1] for the human studies and 2012 OPP Literature Review Guidance[2] for the animal and *in vitro* studies. The quality reviews considered study design, reporting, and sources of bias either inherent in the experimental design or introduced by the study authors in their methodology decisions. All of these factors contributed to the agency's level of confidence in the findings reported in each study. Studies that were of sufficient quality and investigated environmentally relevant exposure scenarios were then evaluated in their respective evidence stream (e.g. human, animal, and *in vitro*) and integrated across lines of evidence in the weight of evidence analysis using the modified Bradford Hill criteria which includes considerations for dose response, temporal concordance, strength, consistency, coherence, specificity, and biological plausibility. The agency's systematic review process, study quality evaluation, weight of evidence analysis, and conclusions are summarized in the HHRA and described in extensive detail in the PD systematic review memo (Wray A. and Niman A., D449106, TXR 0057888, 06/26/2019).

The agency's conclusion that the weight of evidence was insufficient to link paraquat exposure from pesticidal use of US registered products to PD in humans was based on a combination of factors including:

---

[1] US EPA. December 28, 2016. Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides. https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf

[2] USEPA OPP. 2012. Guidance for considering and using open literature toxicity studies to support human health risk assessment.

- large variation in study quality across the evidence streams including several studies with critical deficiencies in study design and/or reporting that affected interpretation and diminished confidence in published results;
- limitations in individual studies and the overall dataset that precluded comprehensive evaluation of dose and temporal concordance in each evidence stream;
- mixed findings, particularly in the animal and human evidence streams, that lowered confidence in positive results;
- weak quantitative and qualitative coherence of PD-like effects across the three evidence streams;
- and a lack of biological plausibility that the *in vitro* and *in vivo* laboratory findings would occur in humans following label-directed use of registered paraquat products.

In addition, the agency also compared the PD-like effects noted in the animal literature with other toxic effects attributed to paraquat and determined that contact toxicity and adverse effects in the respiratory and renal system were the most sensitive effects resulting from paraquat exposure. Therefore, the agency concluded that the established points of departure (PODs) based on these effects would be protective of all paraquat toxicity including the neurotoxic effects reported in the open literature.

Several commenters recommended the agency consider mechanistic data in its evaluation of the link between paraquat and PD and referenced publications reporting subcellular effects as well as the use of paraquat in PD research. The agency did consider mechanistic data in the PD systematic review from relevant *in vitro* publications as well as mechanistic findings reported in *in vivo* studies that utilized an environmentally relevant route of administration. The agency notes that the paraquat model described in the review publications cited in the comments (Tieu 2011; McDowell and Chesselet 2012) elicits PD-like hallmarks in mice through weekly injections of paraquat. Moreover, the Tieu (2011) review describes some inconsistencies in the PD-like response between studies when using the standardized exposure regimen for the paraquat PD model as well as limitations of the model to elicit the same PD hallmarks that are observed in humans. The literature database used for the PD systematic review contained a number of publications that utilize paraquat to induce PD-like hallmarks in animals for PD research and the agency found that most of these publications employed either the paraquat model described above or an exposure regimen that also does not reflect the anticipated paraquat exposure scenarios from pesticidal use (e.g. direct injection into the brain). In the PD systematic review, the agency acknowledged that several publications from the open literature have proposed modes of action (MOAs) to explain how paraquat exposure could lead to PD and that an European Food Safety Association (EFSA) working group published a proposed adverse outcome pathway (AOP) for connecting mitochondrial inhibitors such as paraquat to PD (Terron *et al.* 2018). Accordingly, the agency evaluated cellular and subcellular *in vitro* and *in vivo* mechanistic data that related to these proposed MOAs and incorporated it into the weight of evidence discussion.

The agency identified a large body of evidence demonstrating general neurotoxicity (e.g. general cell viability, mitochondrial dysfunction, oxidative stress, and alterations in the ubiquitin-proteasome system) and PD-specific effects (e.g. dopaminergic neuron viability, α-synuclein formation, and neurochemical changes) across multiple *in vitro* nervous system human and rodent models. However, these data are difficult to translate to *in vivo* effects given that they do not account for chemical-specific toxicokinetics that would dictate the extent to which the chemical can reach the active site in laboratory animals or humans. General toxicity (e.g. oxidative stress, inflammation, and mitochondrial dysfunction) was reported in nervous tissues at the same dose that elicited PD-like hallmarks in several mouse studies that used a risk assessment relevant route of exposure; however, variation in study design (i.e. studies examined different nervous tissues), and inconsistencies in the parameters assessed (i.e. only one study evaluated mitochondrial dysfunction) made it difficult to establish dose and temporal concordance for mechanistic effects and PD-like hallmarks, which would be required to establish a paraquat MOA for the

neurobehavioral/neurodegenerative effects. The agency did not evaluate the AOP proposed in the open literature nor develop one from the data gathered in the systematic review. Given the lack of sufficient evidence for a causal association, the agency did not consider an AOP necessary to characterize paraquat toxicity and evaluate risk for registered products.

Comments on the Conclusions of the Epidemiology Review (Center for Biological Diversity, Pesticide Action Network, Beyond Pesticides, California Rural Legal Assistance Foundation, and Unified Parkinson's Advocacy Council)

EPA Response: In addition to comments on the agency's overall systematic literature review of PD, the agency received several comments on its evaluation of the epidemiologic literature on the relationship between paraquat and adverse health outcomes. This includes comments from the Center for Biological Diversity, Pesticide Action Network, Beyond Pesticides, California Rural Legal Assistance Foundation, and Unified Parkinson's Advocacy Council that emphasized findings from epidemiologic studies that reported evidence of a positive association between paraquat and PD, as well as other health outcomes. Conversely, Syngenta commented on potential omissions in the agency's epidemiology review and discussed risk of bias considerations that may be relevant to the agency's overall weight-of-evidence. Syngenta's comments also included supporting comments from Quality Scientific Solutions, which was requested by Syngenta to evaluate the agency's review of the epidemiology literature on paraquat.

With regard to commenters that emphasized findings from epidemiologic studies that reported evidence of an association between paraquat and PD, several commenters suggested that the agency discounted positive epidemiologic findings from the Agricultural Health Study (AHS) and other study populations. These comments included discussion of the epidemiologic literature on PD, but also included other health outcomes evaluated in the agency's evaluation of the epidemiologic literature on paraquat. The Center for Biological Diversity, for example, commented that a number of epidemiologic studies evaluated in the HHRA, including the AHS, reported positive associations between paraquat and PD, respiratory effects, and other chronic diseases and symptoms. Similarly, the Unified Parkinson's Advocacy commented that there are several more recent studies that reported a positive association between paraquat and PD. While these commenters correctly point out that there are epidemiologic studies that report positive associations between paraquat exposure and PD, as well as other health outcomes, the commenters did not take a holistic account of the evaluation of epidemiologic evidence in the agency's Tier II Epidemiology Report (A Niman, D449108, 6/29/2019). The agency's Tier II Epidemiology Report summarized 74 available epidemiologic studies and included a comprehensive evaluation of study quality and overall evaluation of epidemiologic evidence for PD and a range of the health outcomes examined in the scientific literature. The overall conclusion of the agency's Tier II Epidemiology Report on the evidence on the relationship between paraquat and PD was that there is "limited, but insufficient epidemiologic evidence at this time to conclude that there is a clear associative or causal relationship between occupational paraquat exposure and PD." This conclusion was informed by the positive studies highlighted by commenters, but also reflects mixed findings reported in AHS and a number of study quality limitations related to the design of studies, exposure assessment methods, and potential for bias.

Consideration of Additional Epidemiology Publications and Meta-reviews Not Included in the PD Systematic Review

EPA Response: The Unified Parkinson's Advocacy Council identified one additional epidemiologic study (Caballero *et al.* 2018) that was not evaluated in the agency's systematic review of the relationship between paraquat and PD. The study examined the relationship between residential proximity to agricultural land that may use paraquat and PD-related mortality in Washington State and reported no evidence of a significant positive association between paraquat and PD-related mortality (Ever/Never Paraquat Odd Ratio = 1.22 95% CI: 0.99–1.51). The study utilized Washington State's death registry to

identify deaths for the years 2011-2015 in which the underlying cause of death was PD. The study assessed exposure indirectly using an approach that relied as residential proximity, based on residential address at time of death, to agricultural land that may use paraquat. This exposure assessment approach has several substantive deficiencies that limit the quality of the study. In particular, the investigators relied on a crop-pesticide matrix to identify cropland that may use paraquat. The crop-pesticide matrix was based on general information on crops that use paraquat and did not incorporate any information on the actual spatial location, timing and magnitude of paraquat use in Washington State. The investigators then used a 1000m buffer to assign ever/never exposure to paraquat based on only residential address at time of death. Limited information was provided to justify this buffer distance for paraquat, and no information was provided on whether residential address at time of death can be used to assess potential lifetime exposure. Given these exposure assessment limitations, the study would be considered low quality based on OPP's Epidemiology Framework and would contribute limited weight to the overall body of available epidemiologic evidence on the relationship between paraquat and PD.

Two commenters that emphasized epidemiologic studies that reported an association between paraquat exposure and PD also indicated that there are two systematic reviews published in 2019 that provide additional information that should be considered by the agency (Tangamornsuksan *et al,* 2018; Vaccari *et al.* 2019). The California Rural Legal Assistance Foundation, in particular, commented that the agency's conclusion is "inconsistent with two recently released meta-analyses that are not included in this risk assessment that each strengthen the evidence linking paraquat exposure and Parkinson's disease." HED is aware of these meta-analyses as well as other literature reviews and meta-analyses of epidemiologic studies that were published prior to the public release of the HHRA and Tier II Epidemiology Report (e.g., Breckenridge *et al.* 2016; Friere and Koifmann 2012; Allen and Levy 2013). However, the agency independently evaluated the underlying original ("primary") research findings included in these meta-analyses in its own weight-of-evidence evaluation of the relationship between paraquat exposure and PD. This approach ensures that the agency critically evaluated the available literature and did not rely on the conclusions of external authors that are not subject to the agency's public review process.

While the agency's review focused on its own independent review, the primary difference between the agency's evaluation and the two meta-analyses are methodological with respect to study quality and synthesis of findings. In particular, both articles used different methodologies to assess study quality (i.e., Newcastle-Ottawa quality assessment scale and the modified Newcastle Ottawa Scale, respectively) and reported a statistically significant association between paraquat and PD based on their quantitative synthesis of study findings using meta-analysis. Although there were methodological differences, it is incorrect to conclude that the agency's conclusion on the association between paraquat and PD is inconsistent with the authors of the two meta-analyses. Rather, the conclusions of each meta-analysis are excerpted below and emphasize that while they both reported evidence of an association between paraquat and PD, the available studies that themselves were incorporated into the meta-analysis have substantive limitations and require replication in higher quality studies. These conclusions are similar to the agency's determination that the overall epidemiologic evidence is limited, but insufficient based on somewhat conflicting findings in the AHS cohort, mixed findings in other study populations, and substantive limitations across studies that related to their exposure assessment approach and potential bias that introduces additional uncertainty.

> *Our analysis with new data re-affirms the association of paraquat use with PD. However, objective measurement of paraquat exposure was inadequate and future studies are needed to focus on exposure assessment, disease progression and clinical manifestations thereby providing clues about the mechanism for this insidious disease. Accordingly, further studies to elucidate the effect of paraquat on PD are still warranted especially studies conducted with high quality of exposure assessments in more refined case-control studies.*
> **Tangamornsuksan et al., (2019)**

In summary, positive OR estimates indicate a weak association between exposure to paraquat and occurrence of PD. This association appears to be more evident in individuals exposed to paraquat for extended periods or co-exposed to paraquat and any other dithiocarbamates, although more studies with this information need to be analyzed. The relatively low estimates of risk and low quantity of evidence gathered by this SR and meta-analysis does not enable one to propose a definitive conclusion regarding a causal relationship between paraquat and PD.
Vaccari et al., (2019)

In addition to the commenters that suggested the agency inappropriately discounted epidemiological literature relating to PD and exposure to paraquat, Syngenta commented on potential omissions in the agency's review of the epidemiologic literature and discussion of risk of bias considerations in weighing studies in the overall weight-of-evidence. With respect to omissions, Syngenta indicated that publications from Elbaz *et al.* (2009), Kuopio *et al.* (1999), Rugbjerg *et al.* (2011), Seidler *et al.* (1996), and Semchuk *et al.* (1992) provide information on the association between paraquat exposure and PD but were not included in HED's Tier II Epidemiology Report.

Syngenta is correct that these studies attempted to assess the association between paraquat and PD. As also noted by Syngenta, however, four of these five studies did not report effect estimates because of the small number of PD cases exposed to paraquat (Kuopio *et al.* 1999; Rugberg *et al.* 2011; Seidler *et al.* 1996; and Semchauk *et al.* 1992). These studies, therefore, would contribute limited, if any, weight to the overall body of epidemiologic evidence on the relationship between paraquat and PD. The agency also notes that the exclusion criteria described in its literature search methodology indicate that articles were excluded from review if no risk/effect estimates were reported.

The remaining study by Elbaz *et al.* (2009) considered paraquat exposure in its discussion, but only reported on the association between the quaternary ammonium class of herbicides and PD. The quaternary ammonium class of herbicides includes paraquat as well as other compounds and may not be a reliable surrogate of paraquat exposure alone. No additional information is provided by Elbaz *et al.* (2009) to determine if their study population used paraquat rather than other quaternary ammonium herbicides, including cyperquat, chlormequat diethamquat, difenzoquat, diquat, and mepiquat. As such, Elbaz *et al.* (2009) provides insufficient information to specifically assess the relationship between paraquat and PD and was not included in the agency's evaluation.

Syngenta also commented that the agency's evaluation of the epidemiologic evidence did include the study by Tomenson and Campbell (2011), which examined mortality in an occupational cohort from a UK paraquat manufacturing facility. This study was reviewed in the agency's Tier II Epidemiology Review and was the only study identified that assessed the relationship between paraquat exposure and mortality, including mortality caused by PD. While this study provides information on mortality from PD, there was only a single PD case identified in the study. While Syngenta is correct that the results of the study provide no evidence of an association between paraquat and mortality caused by PD, the study focused on a subset of the 307 deceased workers from a larger cohort of 968 workers. As such, while the study may have some ability to identify deceased workers that had PD, a larger number of workers were excluded from the study (68%) because they were still alive when the study was conducted. For this reason, the agency believes the Tomenson and Campbell (2011) provides only supplemental information on the relationship between paraquat and PD and was not considered in the agency's systematic review. Syngenta also made note that the agency included the AHS study Shrestha *et al.* (2018) in its systematic review even though it focused on the health outcome self-reported dream enacting behavior, rather than PD. While this study was summarized in the agency's systematic review, it was considered supplemental to the AHS studies that directly examined the relationship between paraquat and PD. For example, the agency's review made note that the "relationship between dream enacting behavior and other non-motor symptoms is an area of active research in clinical and epidemiologic research." This focus on the

prodromal PD symptom dream enacting behavior enabled Shrestha *et al.* (2018) to leverage the prospective design of AHS – by focusing on a potential precursor to PD – and provides additional characterization of other AHS studies on PD that focused directly on PD.

Syngenta's comments also suggested that the agency did not fully assess risk of bias in its evaluation of epidemiologic studies and overall weight-of-evidence assessment of the association between paraquat and PD. These comments included more general considerations on potential selection bias in case-control studies that recruit controls from hospitals and family/friends of cases, relative importance of statistical power and risk of bias, and terminology used to describe case-control studies (hospital vs. population-based studies). Syngenta also provided more specific comments on the agency's study quality assessment. This included additional evaluation considerations on the AHS-FAME Study that was rated as being high quality by the agency, five case-control studies rated as being moderate quality by the agency (Liou *et al*. 1997; Tanner *et al.* 2009; Costello *et al.* 2009; Brouwer *et al.* 2017; van der Mark *et al.* 2014), and one case-control study being rated as low quality by the agency (Firestone *et al.* 2005; 2010).

With regard to the agency's quality assessment of the AHS-FAME Study, Syngenta commented that the AHS-FAME Study did not warrant a high-quality rating because of recall bias and potential selection bias. The agency considered risk of bias in its assessment of the AHS-FAME Study but designated it as high quality because the nested case-control design, nested with the AHS, enabled the investigators to examine the association between paraquat use and PD in well characterized agricultural populations in Iowa and North Carolina. This study design also allowed the investigators to consider demographic and lifestyle factors that could act as confounders and examine potential effect modification of genetic factors and occupational hygiene practices. While the agency rated the AHS-FAME as high quality, its findings on the association between paraquat and PD are not definitive and are subject to substantive limitations that were summarized in the agency's evaluation. In particular, the agency noted that there were conflicting findings with respect to incident and prevalent PD cases within the AHS. The AHS-FAME study also may have introduced additional recall bias by conducting a separate exposure assessment after cases and controls were enrolled in the study. As such, the agency considered the strengths and limitations of the AHS-FAME Study in its overall conclusion that there is limited, but insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between occupational paraquat exposure and PD.

Syngenta's comments on five case-control studies rated as being moderate quality by the agency (Liou *et al*. 1997; Tanner *et al.* 2009; Costello *et al.* 2009; Brouwer *et al.* 2017; van der Mark *et al.* 2014) and one case-control study being rated as low quality by the agency (Firestone *et al.* 2005; 2010) will not substantively change the agency's overall conclusions on the available epidemiologic evidence. In characterizing its overall conclusion, the agency made note that these studies yield mixed results with respect to potential occupational and non-occupational exposure and may also be subject to recall bias, limitations in their exposure assessment approach, and potential selection bias. Similarly, Syngenta's comments on the study quality assessment of Firestone *et al.* (2005; 2010) will not change the agency's overall conclusions because the study only had two paraquat exposed PD cases and contributed limited weight in the agency's overall evaluation.

Consideration of Additional Animal and *In Vitro* Publications Not Included in the PD Systematic Review

EPA Response: Additional animal and *in vitro* publications were identified in the public comments that were not included in the literature database compiled for the PD systematic review. The registrant, Syngenta, also submitted four additional industry funded non-guideline studies (identified with MRID numbers below) after publication of the HHRA. The agency reviewed all newly identified and submitted studies and concluded that they would not impact the PD systematic review conclusions. Most of the

additional laboratory animal publications and non-guideline studies administered paraquat via injection into the peritoneal cavity [Chinta *et al.* 2018; Marks 2007a (MRID 50958001, unpublished); Marks 2007b (MRID 50958002, unpublished); Marks 2007c (MRID 50958003, unpublished)] and one study perfused paraquat directly to the substantia nigra (Tamano *et al.* 2019). As stated above, injection is not a relevant route of exposure for pesticidal uses of paraquat and cannot be used to evaluate toxicity and risk for anticipated exposure scenarios. Direct perfusion to the substantia nigra is, likewise, not a relevant exposure pathway. Studies that administered paraquat via injection or perfusion are also of limited utility as mechanistic information given the lack of conclusive evidence that oral, dermal, or inhalation exposure elicits the same PD-like effects in animals reported in these studies. The toxicity data reported in these studies are, therefore, not pertinent to evaluating the connection between exposure from paraquat pesticidal use and PD. One study submitted by Syngenta [Ray 2011 (MRID 50958004, unpublished)] quantified paraquat in cortical brain tissue collected from spider monkeys. The brain tissue samples were provided to Syngenta by SRI International and were collected as part of a separate study conducted at SRI International to investigate the effects of paraquat on nigrostriatal function/integrity. The original study was conducted 3-4 years prior to the brain tissue analysis during which time the tissues were kept in frozen storage. Although the study demonstrated quantifiable concentrations of paraquat in brain tissue, the study report did not indicate the route of administration nor dosing regimen in the original study. The agency thus could not utilize these data to further characterize paraquat toxicokinetics in monkeys.
One additional *in vitro* study was referenced in the comments (Colle *et al.* 2018) that was not included in the PD systematic review literature database because it was published after the final open literature search conducted for the PD systematic review. The agency reviewed this study and determined that while it does report relevant *in vitro* mechanistic information, the findings were consistent with *in vitro* paraquat effects already discussed in the PD systematic review and, as a result, do not alter the agency's overall conclusion from the PD systematic review.

II. Endpoint and uncertainty factor selection

The EPA Did Not Adequately Explain Why the Acute and Chronic Points of Departure Were Updated and They Are Not Health Protective (Pesticide Action Network)

EPA Response: The Pesticide Action Network expressed concerns that the updated acute and chronic dietary points of departure (PODs) were not adequately explained and not health protective. The rationale for updating the dietary PODs is described in Section 4.5 in the paraquat HHRA (Britton W. *et al.,* D430827, 06/26/2019) and is summarized here for reference.

The acute dietary POD (5 mg paraquat ion/kg) was updated for the most recent risk assessment because the POD (1.25 mg paraquat ion/kg) used in the previous risk assessment (T. Morton, D415809, 08/25/2014) was not based on an acute effect (e.g. the lung response in the rat multigeneration study was observed during the histopathology analysis at the end of the study and could not be unequivocally attributed to a single dose). The agency considered the acute mortalities and associated clinical signs in the developmental study in rats to be the most appropriate effect for the acute dietary POD because it was consistent with evidence in other acute oral studies and human incident reports of delayed symptoms and lethality from acute exposure and was protective of other acute effects noted in the database and in the open literature. As discussed in the HHRA, the agency identified a study from the open literature (Lou *et al.* 2016) that was both acceptable for use in risk assessment and reported findings relevant to the risk assessment (e.g. delayed acute mortality, age-related sensitivity, and behavioral changes). The agency initially considered the literature study for the acute dietary POD, but ultimately selected the guideline developmental study because the agency had more information on the methods for the guideline study including analytical results for the dosing solution (concentration and stability), the agency could review all individual animal data for the parameters assessed, and the paraquat product used in the guideline study was thought to be more representative of the available technical and end-use products. It was not

the agency's position that the findings in the literature study were unrelated to paraquat. Rather, the agency considered that the lack of similar findings in the guideline studies might be related to the lower purity compounds used in those studies and thus the findings from the guideline studies would be more reflective of toxicity from the commercially available pesticide products that were ≤48% paraquat. However, further review of the original guideline studies revealed several transcription errors in the data evaluation records and it was determined that several guideline studies did, in fact, use the high purity paraquat dichloride including the developmental rat study used for the acute POD.

Based on this discovery the agency re-evaluated the Lou *et al.* (2016) study. Originally the study was classified acceptable for quantitative use; however, in a recent follow-up communication with the authors they mentioned that they were not able to analytically confirm the concentration of the dosing solutions during the study. The agency is still of the opinion that the study was well conducted; however, the lack of analytical confirmation has introduced uncertainty to the dose response assessment and lowered confidence in the quantitative findings of the study as the agency could not confirm whether the actual concentrations were similar to the reported nominal concentrations. The findings from this study are still considered to be related to paraquat treatment; however, the uncertainty in the exposure concentrations precludes the agency from considering the findings quantitatively in the POD selection and uncertainty factor determination. Given this uncertainty, the agency reclassified this study as acceptable for qualitative use only. This re-evaluation reinforced the original conclusion that the acute effects in the developmental study were the most robust acute endpoint of the acute toxicity data available and, therefore, the most appropriate study to establish the acute POD.

The agency revised the chronic dietary POD from 0.45 mg paraquat ion/kg/day (NOAEL from the subchronic dog study) to 0.5 mg paraquat ion/kg/day (NOAEL from the chronic dog study) because the two dogs studies reported similar respiratory effects, the NOAELs were similar, and selecting the slightly higher NOAEL from the chronic dog study was still health protective of the toxicity noted in both dog studies as well as other effects reported in the paraquat toxicity database and the open literature.

The EPA Should Reconsider the Selection of a Respirable POD for the Inhalation Assessment (Syngenta)

EPA Response: One of the paraquat registrants, Syngenta, disagreed with the agency's decision to conduct an inhalation assessment using a POD based on upper respiratory effects reported in the guideline inhalation study. Their comments expressed that a non-respirable particle POD was more appropriate, but also that they concurred with a previous agency conclusion that an inhalation risk assessment is not warranted . Their rationale for not using the POD from the rat inhalation study and for not conducting an inhalation assessment was that application equipment commonly used for applying aqueous non-selective herbicides do not produce droplets in sizes that fall within the respirable range tested in the subchronic rat inhalation study used to establish the inhalation POD for the HHRA. Syngenta referred to an analysis of open literature data that indicated spray equipment used for aqueous non-selective herbicides produce larger particles ranging from 200-400 µm in order to improve coverage of target species and minimize spray drift. In addition, Syngenta submitted summary and raw data from a 2009 study conducted in Brazil that demonstrated simulated terrestrial application of water and several paraquat formulations using common nozzle sizes and pressure settings produce spray droplets with volume median diameter >200 µm, size range from 220-340 µm. The study also reviewed water droplet size distribution data compiled in the AgDRIFT® library for aerial applications which demonstrated a volume median diameter >200 µm, size range from 218-457 µm for a range of common nozzles. Based on these data, the study authors concluded that terrestrial and/or aerial application of paraquat using these nozzles would result in a very small proportion of respirable or inhalable droplets and thus negligible inhalation exposure.

The agency notes that, contrary to Syngenta's comment, inhalation risks were assessed in previous paraquat risk assessments using a "non-respirable" POD that was based on effects reported in an oral study. Moreover, the agency recognizes that it mischaracterized the "respirable" POD selected for assessing inhalation risk in previous assessments as well as the draft risk assessment for registration review. The most sensitive effects reported in the guideline inhalation study that were used to establish the inhalation POD were noted in the extra-thoracic region of the respiratory system. These effects in the upper respiratory tract were the result of exposure to a polydisperse distribution of aerosols that includes droplets in the inhalable range for the rat. Consequently, the "respirable" descriptor used for the inhalation POD in the risk assessment is not accurate and the inhalation POD actually accounts for and is protective of exposure to aerosols in the inhalable range, which includes respirable droplets.

Although the data from the 2009 study support Syngenta's assertation that a majority of the spray droplets produced from these nozzles will be larger than the 1-3 µm droplets produced in the guideline inhalation study, the agency cannot assume in its assessment that every paraquat applicator will use the nozzles tested in these studies. The agency also notes that 3-17% of the droplets produced were in the inhalable range indicating inhalation exposure is not negligible when using the two nozzles tested in the 2009 study. Evaluation of spray nozzle data used for spray drift analyses indicates that aerosols in the inhalable range are produced regardless of spray quality, but that the fraction of droplets in the inhalable range decreases for spray nozzles designed to produce coarser particles. As part of registration review, Syngenta is proposing to add language to the existing and new product labels that will require use of large nozzles with their products to minimize the production of inhalable or respirable droplets; however, there is no indication that other registrants intend to apply similar requirements to their product labels. The agency further notes apparent inconsistencies between the air monitoring and droplet size data referenced by Syngenta and human incidents involving inhalation exposure. In a memo from 2000 (J. Blondell; D260797; 08/10/2000), the agency evaluated the frequency of incidents associated with inhalation exposure reported in the Poison Control Center data from 1993-1998 and the open literature and remarked on the apparent disconnect between these incidents and findings from the National Institute for Occupational Safety and Health (NIOSH) and others that suggested respirable levels of paraquat produced under normal circumstances would not be sufficient to cause poisoning. While no reason for the discrepancies between incident and exposure data could be determined, the agency expressed concern in its conclusions that even nasal exposure to non-respirable droplets could result in serious or fatal poisoning given that larger paraquat droplets could be retained in the nasal mucosa and that nosebleeds – an effect associated with exposure to paraquat spray droplets and dust – could enhance absorption across nasal membranes. In addition, the Tier II incident report (E. Evans and S. Recore, D446902, 07/25/2018) composed for registration review describes incidents occuring between 1998 and 2018 reported in several incident databases that were attributed to inhalation exposure as well as symptoms of respiratory irritation and upper respiratory pain following exposure which are distinct from the systemic lung effects noted in the animal studies following oral exposure. These incidents suggest that paraquat use produces droplets that are at least in the inhalable range – a conclusion that is supported by the droplet size data from the 2009 Syngenta study – and results in appreciable inhalation exposure and adverse portal-of-entry effects. . The agency acknowledges that the discrepancies are difficult to reconcile given that route of exposure is not always confirmed for incidents; however, it does reduce the agency's confidence that the open literature droplet size data accurately reflect exposure for all paraquat uses.

The agency cannot rule out the potential for inhalation exposure from paraquat use based on the findings reported above; therefore, an inhalation assessment is warranted for the paraquat registration review. Conducting an inhalation assessment for paraquat using only an oral POD, consistent with previous risk assessments, would not account for the potential of portal of entry toxicity in the upper respiratory tract tissues resulting from inhalable particles for a chemical that is known to be corrosive to skin and mucus membranes and that animal studies and human incidents suggest is a possible consequence of paraquat use. Given the uncertainties outlined above, the agency considers the POD selected in the paraquat

HHRA based on upper respiratory effects in the rat inhalation study to be more appropriate for assessing inhalation risk, particularly for route-specific portal of entry toxicity, and thus will retain it for the inhalation risk assessment.

The EPA Should Reconsider the Uncertainty Factors Applied to the Dermal POD (Syngenta)

EPA Response: Syngenta recommended that the agency consider reducing the interspecies factor (UF_A) for the dermal POD from 10X to 3X because using the rabbit as a model for paraquat dermal toxicity is overly conservative for evaluating dermal irritation, skin damage, and predicating systemic toxicity. The agency does not agree with this proposal. The agency does have policies and practices in place that allow for reduction of the interspecies uncertainty factor for different exposure scenarios when there are well established pharmacokinetic (e.g. human equivalent calculations for inhalation studies) and/or pharmacodynamic (e.g. thyroid effects in rats) differences between model species and humans. These policies or practices are developed through comprehensive review of a robust body of evidence and are data driven. The agency routinely uses animal dermal studies, usually performed with either rats or rabbits, to evaluate risks for dermal exposure; however, it does not have a policy or practice in place to reduce the uncertainty factors based on interspecies differences in skin penetration. The agency does not consider the current evidence on interspecies differences in paraquat dermal absorption to be robust given that there is limited dermal toxicity information available and the dermal penetration literature does not adequately address the influence of paraquat's corrosive properties.

The rabbit dermal toxicity study is the only guideline study available to evaluate paraquat toxicity from dermal exposure. The agency acknowledged in the risk assessment that there were no systemic effects noted at the highest dose tested in the rabbit dermal study and established it as the systemic NOAEL for the study. The lack of systemic effects suggests that dermally applied paraquat was unable to reach systemic circulation even at the highest dose tested where progressive skin lesions were noted, which is consistent with human dermal penetration data for this chemical. Yet, a LOAEL for systemic toxicity could not be established because the study authors elected not to test at a higher dermal dose due to welfare concerns for the animals. Given the dose response observed for the skin lesions in rabbits, it is likely that higher doses would further erode the skin layer, resulting in increased dermal absorption and associated systemic toxicity. Though aspects of the study design may have influenced the extent of dermal irritation and damage, there are no other studies available to evaluate dermal or systemic toxicity from repeat dose dermal exposure at doses above those tested in the rabbit dermal study. This introduces considerable uncertainty in estimating human risk for dermal exposure.

The agency agrees with Syngenta that the available evidence indicates paraquat is poorly absorbed across intact human skin; however, evidence of severe dermal toxicity in human incidents also suggests that paraquat can affect the integrity of human skin after prolonged dermal exposure. The dermal dose that resulted in skin damage reported in these human incidents is not clear, but it is evident that paraquat can elicit mild to severe dermal toxicity in humans. Given the uncertainties from the laboratory animal toxicity study, the agency recommended in the risk assessment that the registrants conduct a skin irritation assay to better understand how paraquat interacts with human skin at dermal doses above those tested in the human dermal absorption study. With the currently available data, the agency elected not to use the previous oral POD to estimate an equivalent dermal dose because it does not account for potential changes in skin permeability with increasing dermal dose.

Syngenta referenced several studies from the open literature (Bartek *et al.*, 1972; Scott *et al.*, 1986; Phillips *et al.*, 1972) to support their conclusion that the rabbit model is overly conservative. The agency did not have access to the raw data for these studies to confirm the findings reported and in one case (Scott *et al.*, 1986) could not access the full text of the study. Regardless, the findings reported in these studies, whether in the abstract or in the text, did not demonstrate unequivocally that the rabbit is a

conservative model for paraquat dermal toxicity. The studies suggest that systemic absorption would be greater in rabbits compared to humans across intact skin; however, they do not address species differences in skin corrosion and the irritation study (Phillips *et al.*, 1972) focused on species differences for acute exposure rather than repeat dose exposure. The findings in these studies do not address the agency's concern that repeat dermal exposure in humans would cause the same progressive damage to the epidermal layer that was observed in rabbits and would lead to enhanced absorption at dermal doses above those investigated in the human dermal absorption study and the current dermal POD. The agency will, thus, retain the current dermal POD and the 10X uncertainty factors for interspecies extrapolation and intraspecies variation to be protective of the potential for systemic toxicity from skin corrosion at higher dermal doses.

EPA Should Retain the Food Quality Protection Act (FQPA) Safety Factor (SF) for the Paraquat HHRA (Center for Biological Diversity, Environmental Working Group, and Pesticide Action Network)

EPA Response: The Center for Biological Diversity, Environmental Working Group, and Pesticide Action Network expressed concern with the Agency's decision to reduce the FQPA SF to 1X and singled out the age sensitivity findings in the Lou *et al.* (2016) study and that the agency did not account for neurotoxicity effects in the POD selection as evidence for retaining the FQPA SF. The PODs selected in the paraquat HHRA to evaluate dietary, occupational and non-occupational risks were all below the lowest dose tested in the Lou *et al.* 2016 study (5 mg paraquat dichloride/kg/day), with the exception of the acute POD. As stated above, the uncertainty in the exposure levels reported in the Lou *et al.* (2016) study precluded using it quantitatively for risk assessment and, therefore, could not be considered in selection of the acute POD. Moreover, the agency's confidence in the evidence of age-related sensitivity is affected by the uncertainty in the actual concentration administered to the different age groups, as it was not analytically confirmed by the study authors. No other evidence of lifestage sensitivity was observed in the guideline studies nor in studies from the open literature that investigated toxicity at or below the current PODs. In addition, as detailed in several other responses, the agency conducted a thorough systematic review of the paraquat open literature to identify toxicity information that were not captured in the guideline and non-guideline studies submitted to the agency including evidence of PD effects in humans and PD-like hallmarks in animals. After reviewing all relevant data, the agency determined that the respiratory and contact toxicity effects used to establish the current PODs were the most sensitive effects reported following exposure to paraquat. Given lower confidence in the finding of age-related sensitivity reported in the open literature, the lack of evidence of pre- or postnatal sensitivity in the guideline studies, and that the PODs were based on the most sensitive effects observed following paraquat exposure, the agency is confident the current PODs are protective of all lifestages and supports a reduction in the FQPA SF to 1X.

One commenter also mentioned that the agency had retained a 3X FQPA SF in previous risk assessments. The agency had retained the 3X for acute dietary risk assessments conducted prior to 2012 based on the lack of a non-rodent developmental study; however, the agency determined in 2012 (Rury K., TXR 0056294, 04/12/2012) that a non-rodent developmental study was not likely to add information that would impact the paraquat risk assessment and thus the lack of this study was no longer considered a database gap. This decision was one of several considerations, including those outlined above, in the agency's decision to reduce the FQPA SF to 1X.

The EPA Did Not Account for Combined Inhalation, Dermal, and Oral Exposure in its Assessment (California Legal Assistance Foundation and Pesticide Action Network)

EPA Response: The California Legal Assistance Foundation and Pesticide Action Network questioned why the agency did not combine inhalation exposure with the dermal and oral exposures for the

occupational risk assessment. In accordance with HED policy, oral, dermal, and inhalation exposure can only be combined if the PODs are based on the adverse effects in the same target organs/systems. For paraquat, inhalation exposure estimates cannot be combined with dermal and oral exposures because the inhalation POD is based on portal of entry toxicity that is unique to the inhalation route of exposure. Commenters also expressed concerns that the inhalation POD did not account for systemic effects that could result from paraquat inhalation. Portal of entry effects were the most sensitive response to repeated paraquat inhalation exposure in the inhalation guideline study. The study did not include hematology or clinical chemistry evaluations nor conduct gross or histopathological evaluations on non-respiratory tissues. Nevertheless, the lungs were evaluated in this study and lung effects were commonly the most sensitive systemic effect observed in rats in the paraquat toxicity database. No lung effects or mortalities were observed at the lowest concentration level that elicited portal of entry effects suggesting that paraquat absorption in the respiratory tract and/or clearance to the gastrointestinal tract was not contributing to toxicity at the lowest-observed-adverse-effect-level (LOAEL) established for this study. Mortality and lung effects were only noted at higher inhalation concentrations. In selecting a no-observed-adverse-effect-level (NOAEL) based on portal of entry effects as the POD, the risk assessment accounts for and is protective of the subsequent systemic effects reported at higher concentrations.

The EPA Did Not Consider Open Literature Data in POD Selection (Center for Biological Diversity and Environmental Working Group)

EPA Response: The Center for Biological Diversity and Environmental Working Group expressed concern that the agency was using outdated guideline studies, ignored peer-reviewed studies from the open literature, and did not consider effects reported in the literature, including neurotoxicity, in the paraquat HHRA. As part of the paraquat registration review, the agency conducted a general review of the open literature for all reported effects. The goal of this review is to capture a broad selection of the paraquat open literature by searching based on chemical name and common animal models and not date limiting the search. The publications returned from our search strategy include studies conducted up to 2018 and thus provide more recent toxicity data for paraquat to complement the data available from the guideline studies. In addition, the agency conducted a general epidemiology systematic review as well as a systemic review of human, animal, and *in vitro* publications that reported neurotoxic effects from exposure to paraquat with a focus on PD and PD-like responses. Between the three reviews, the agency screened 11,713 studies (**Note: this is not the number of unique publications as the search strategies overlapped resulting in a number of duplicates**).

Studies identified as relevant to evaluating human health risk from paraquat pesticidal use were individually evaluated for quality and substance. The quality assessment for open literature studies was conducted in accordance with the OPP Epidemiology Framework for the human studies and 2012 OPP Literature Review Guidance for the animal and *in vitro* studies. The agency's evaluation considered study design, reporting, and sources of bias when interpreting the findings reported in each study. The agency uses the recommendations in the toxicity study guidelines as a starting point in the review; however, an open literature study does not have to include every aspect of the guideline study to be considered for risk assessment. The agency also took into account the relative impact of each deficiency to determine if it would only affect a subset of the data presented (e.g. bias in analysis of a particular parameter) or diminish confidence in the entire study (e.g. inadequate sample size or the identity and purity of the product was not reported or could not be deduced from the information provided in the publication). Publications were considered unacceptable for use in risk assessment only when its deficiencies diminished all confidence in the reported conclusions. In studies deemed acceptable for risk assessment, the agency then evaluated the substance of the findings relative to the information already reported in the agency's paraquat toxicity database. As part of the substance evaluation, the agency compared the effect level to the POD selected for risk assessment and determined whether the effects reported were biologically significant and adverse. Studies that reported unique effects not covered in the HHRA, but

only at doses above the current PODs, contributed qualitative information to the paraquat hazard characterization but did not have a quantitative impact on the risk assessment. The findings from these literature reviews were summarized in the HHRA and are discussed in more detail in their respective documents (Wray A. and Niman A., D449106, TXR 0057888, 06/26/2019; Wray A., D449107, TXR 0057887, 06/26/2019; Niman A., D449108, 06/26/2019).

All relevant, acceptable laboratory animal publications identified in the open literature reviews as well as the conclusions of the epidemiology and PD systematic reviews were considered with the guideline studies in selecting PODs and UFs for the paraquat HHRA. After reviewing all of the available data including the risk assessment relevant neurotoxicity studies in mice, the agency determined the respiratory effects and contact toxicity noted in the guideline studies were the most sensitive effects reported in animal studies from repeated exposure to paraquat for all routes of exposure and for all lifestages. Accordingly, the agency established the repeat dose PODs based on respiratory and contact toxicity effects. The HHRA, therefore, accounts for and is protective of all reported paraquat toxicity in the guideline studies and the open literature including the PD-like hallmarks observed in laboratory animals at higher dose levels. Moreover, the agency determined that additional UFs were not warranted to be adequately protective of neurotoxicity and other health effects associated with paraquat exposure given that the PODs were based on the most sensitive effects reported for paraquat and the lack of sufficient evidence to suggest a causal or associative relationship between exposure and health outcomes investigated in the epidemiology literature.

III. Co-exposures and mixtures

The EPA Should Consider Co-Exposures to Paraquat, Its Metabolites/Degradates, and Other Pesticides in the HHRA (Center for Biological Diversity, the City of Sacramento, and the California Legal Assistance Foundation)

EPA Response: The Center for Biological Diversity, the City of Sacramento, and the California Legal Assistance Foundation recommended that the agency consider co-exposures of paraquat with other pesticides in evaluating the link between paraquat exposure and PD as well as in the overall evaluation of human health risks from paraquat pesticidal uses. The agency does not assess human health risks from mixtures or co-exposures with the exception of chemicals that exhibit a common mechanism of toxicity and/or chemicals that produce a toxic metabolite or degradate that is shared by other chemicals. At the time the HHRA was completed, the agency had not made a common mechanism of toxicity finding for paraquat nor did the agency identify a toxic metabolite/degradate produced by other substances. The agency, therefore, did not assume paraquat had a common mechanism with other substances and a cumulative assessment was not conducted. The City of Sacramento also recommended the agency consider co-exposures to the parent compound and its metabolites, degradates, and transformation products formed in the environment and/or during wastewater treatment. As part of registration review, the agency determined that no major metabolites or degradates were formed from registered uses of paraquat products that would be considered residues of concern in food and/or drinking water. Therefore, the HHRA evaluated risk for exposure to paraquat only.

IV. Endocrine Disruption

The EPA Did Not Adequately Assess the Potential for Paraquat to Cause Endocrine Disruption (Beyond Pesticides and the Center for Biological Diversity)

EPA Response: Beyond Pesticides and the Center for Biological Diversity expressed concerns that the paraquat HHRA did not fully assess the potential for endocrine disruption from paraquat exposure. As part of registration review, the agency reviews numerous studies that investigate general systemic toxicity

following acute, subchronic, and chronic exposure, as well as several studies that focus on particular systems including the reproductive system. Most of these studies evaluate endpoints that may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. In its review, the agency did not find any evidence of endocrine disruption in either the general toxicity guideline studies or those more focused on the endocrine system (e.g. multi-generation reproduction study).

Paraquat was not included on either list of chemicals selected for EDSP screening; however, the agency does conduct a general literature review for all reported effects, including endocrine disruption in laboratory animals and human studies as part of registration review. This review captures a broad selection of the paraquat open literature by searching based on chemical name and common animal models and not date limiting the search. The publications returned from our search strategy include studies conducted after the guideline studies and thus provide more recent toxicity data for paraquat. The agency screened 3,971 studies for the general paraquat open literature review and more thoroughly reviewed 26 (17 of these studies were separately identified in the PD systematic review that screened 7,166 publications) that reported unique information with a potential to impact the risk assessment. None of the peer-reviewed published studies screened and reviewed reported evidence of endocrine disruption at dose levels below the current points of departure (PODs) used to assess dietary, occupational, and non-occupational risks. In addition, a general epidemiology review of the open literature was conducted that screens 576 publications. Several epidemiology studies were identified in this screen that examined health outcomes related to endocrine disruption (e.g. thyroid disruption and male reproduction). The agency identified several limitations in these studies including their cross-sectional design and classified them as low quality in accordance with the OPP Epidemiology Framework. Consequently, the agency determined that there was insufficient evidence to conclude that there is a clear associative or causal relationship between paraquat and the endocrine disruption health outcomes. Given the lack of endocrine disruption findings at or below the current PODs and insufficient evidence in the epidemiology literature, the agency is confident the HHRA adequately accounts for and is protective of potential endocrine disrupting effects that could result from exposure to paraquat.

V. Residential and Occupational Risk Assessments

EPA Overestimates the Efficacy of Protective Clothing and Engineering Controls *(*California Rural Legal Assistance Foundation, Farmworker Association of Florida and Farmworker Justice and the environmental organizations Earthjustice, Toxic Free NC and Pesticide Action Network):
The data utilized in the occupational handler assessments are based on exposure monitoring studies where workers/handlers wore typical clothing and recommended personal protective equipment (PPE) as they normally would. Therefore, the risk estimates for the different exposure scenarios are representative of current practices and potential exposures under real world conditions. During the risk management process, consideration is given towards not only the risk estimates provided in the human health risk assessment, but also on the impact of PPE (e.g., heat stress, etc). It is acknowledged that engineering controls provide a higher level of protection compared with PPE, and this is also considered when making risk management decisions.

The Worker Protection Standard (WPS) is very clear in section 170.507(b) on the requirement that the employer provide PPE to employees: "Employer responsibilities for providing personal protective equipment. The handler employer must provide to the handler the personal protective equipment required by the pesticide product labeling in accordance with this section. The handler employer must ensure that the personal protective equipment is clean and in proper operating condition..."""... if an employer fails to provide the handler with the label information, which includes the

information about the PPE they must wear, they are in violation of the WPS, which constitutes an unlawful use of the pesticide."

EPA Response: EPA agrees with the comment. The WPS requirements for employers to provide the necessary protective equipment as assessed in the occupational handler assessment and as required by product labeling is necessary for protection of human health. Failure of an employer to supply the necessary label-required PPE is inconsistent with WPS Section *170.507(b)*and could result in an increased risk potential for the occupational handlers exposed.

Failure to Account for Exposure from Inhalation of Paraquat-Contaminated Dust (California Rural Legal Assistance Foundation, Farmworker Association of Florida and Farmworker Justice and the environmental organizations Earthjustice, Toxic Free NC and Pesticide Action Network):
USEPA's failure to analyze the risk of exposure to paraquat from dust undermines the validity of the risk assessment. Paraquat has a low vapor pressure and adheres strongly to soil clays, does not photodegrade and is resistant to microbial degradation. In the assessment, USEPA acknowledges that "There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and particles that contain pesticides." The assessment includes the explanation that during Registration Review, the Agency will use the Volatilization Screening Analysis to determine if data or further analysis is needed for paraquat. Notably, assessment of exposure through dust is not mentioned. Failure to include an assessment of the risks associated with inhalation exposure from paraquat contaminated dust for post-application workers and farmworkers in paraquat treated fields and for bystanders and those living in farmworker housing near treated fields is a serious omission in this assessment that underestimates exposure and thus underestimates risk.

EPA Response: The agency acknowledges the potential for paraquat adherence to soils and subsequent inhalation of dusts as these are generated during post-application activities in previously treated fields. Occupational exposures to paraquat from handling activities (i.e., mixing/loading, application, and mixing/loading/application) are expected to be greater than any potential exposures to dusts. Therefore, the assessment of the inhalation exposures from the occupational handling of paraquat products is protective of any potential inhalation exposure from dusts which are not believed to be a significant exposure source.

EPA Must Take into Account Real-World Scenarios (Center for Biological Diversity)
The EPA often claims that it is acting conservatively by using the maximum labeled use rates when estimating exposure to plants and animals. These upper-level exposure scenarios, however, do not take into account accidental spills and illegal uses of the pesticide. An assumption of 100 percent label compliance underestimates risk and is unsupported by state-collected data. EPA even discounts incident data if there was the possibility that the pesticide was not used in accordance with the law, even though it was demonstrated to happen.

The data that are available on label compliance indicate that it is unreasonable to assume that pesticides are always applied in accordance with the label or with proper PPEs. We feel that when communicating findings to a risk manager, the EPA should no longer refer to its use of maximum labeled rates as "conservative" or accurately estimating peak exposures that may occur. And modeling of maximum use rates should absolutely never be used to discount level of concern ("LOC") or population adjusted dose ("PAD") exceedances.

EPA Response: EPA assesses potential exposures and risks to pesticide products assuming that the product user, whether occupational or residential, reads the product label and follows any label directions and heeds all safety precautions with use of the product. A critical function of the product label is to manage the potential risks as identified by EPA's assessment. It is a violation of Federal law to use a pesticide product in a manner inconsistent with its labeling. Therefore, the potential illegal usage of pesticide products is not quantitatively assessed by EPA.

EPA acknowledges that there is the potential for accidental spills and accounts for this risk assessment consideration through the evaluation of reported incident information from multiple sources including: the National Pesticide Information Center (NPIC); NIOSH's Sentinel Event Notification System for Occupational Risk (SENSOR); American Association of Poison Control Centers; information submitted directly to EPA, and voluntary reporting through by the public. In addition, pesticide registrants (i.e., the manufacturers of pesticide products) are required by law to submit to the EPA reports of adverse effects from usage of their products. EPA's incident report evaluation helps the Agency to determine whether the pesticide's application directions require clarification, some uses of a pesticide should be limited, or whether additional personal protective equipment (PPE) should be required.

Based on the high number and severity of human health incidents reported for the ingestion of paraquat, both accidental and intentional, the EPA determined that risk mitigation measures were necessary for paraquat pesticide products to meet the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) standard for registration. This mitigation decision[1] was published in January 2017. The following mitigation measures were implemented in three phases. Submission deadlines and implementation timeframes for these measures are discussed below.

1. Label amendments to emphasize paraquat toxicity and restrict use of all paraquat products to certified applicators only (i.e., prohibiting use by uncertified persons working under the supervision of a certified applicator), and supplemental warning materials
    a. Implementation timing:
        i. Revised labels and supplemental materials were submitted to EPA in March 2017
        ii. Revised labels and supplemental materials were stamped approved by EPA in late Summer/Fall 2018
        iii. New products released into commerce must bear this new labeling by late Summer/Fall 2019

2. Targeted training materials for paraquat users
    a. Implementation timing:
        i. Released online in March 8, 2019
        ii. New products released into commerce must bear new labeling specifying the requirement to take the targeted paraquat training by late Summer/Fall 2019

3. Closed-system packaging for all non-bulk (less than 120 gallon) end use product containers of paraquat
    a. Implementation timing:
        i. Revised labels specifying the closed system requirement were due to EPA on March 29, 2019
        ii. The revised labels are currently under review in EPA and should be stamped in Summer/Fall 2019

[1] M. Mannix. Amended: Paraquat Dichloride Human Health Mitigation Decision. January 12, 2017. *This document supersedes the December 14, 2016 Paraquat Dichloride Human Health Mitigation Decision.*

iii. All non-bulk products must be in closed systems one year from the date that the labels are stamped by EPA
iv. EPA's existing stock provision applies

Lack of Clarity Relating to the Level of Personal Protective Equipment Assumed for Occupational Handler Risks Assessed (National Cotton Council)
It is unclear if EPA is stating that both the existing (occupational handler) PPE and the amended label additions, such as the closed-system packaging, were included together in the risk assessment or viewed separately. The NCC believes the assessment should be reflective of all requirements based on the current label and urges EPA to verify this is the case.

EPA Response: The occupational handler exposure scenarios assessed for paraquat were quantified for various levels of PPE or engineering controls. Results for the paraquat risk assessment were presented starting at the lowest levels of PPE (mixers, loaders, and applicators and other handlers to wear baseline clothing, chemical resistant gloves, and a NIOSH approved half-mask, PF10 respirator) required by the product labels for each exposure scenario. Engineering controls, consistent with the closed system requirements, were assessed separate from the assessment of label-required PPE.

Lack of Clarity Relating to the Inhalation Exposure Assessment (National Cotton Council)
The NCC asks for greater clarity related to the inhalation exposure component of the risk assessment. Technology has dramatically improved worker environments with closed cab equipment and filtered air conditioning. The NCC requests clarity if the assessment accounts for these technologies.

EPA Response: EPA's assessment of occupational post-application exposures and risks from cotton harvesting are based on transfer coefficient (TC) data derived from a study which measured exposures resulting from conventional harvest practice and associated activities. The paraquat occupational post-application assessment also considered the submission of summary information from a 2016 survey by the National Cotton Council[3] and an October 18, 2018 meeting with OPP and the National Cotton Council. While this information suggests that technology is moving increasingly toward the newer mini-module harvesters, the conventional harvest practice remains in use by approximately half of the survey participants. EPA acknowledges that the newer mini-module harvester, as well as new technologies such as closed cab filtered air conditioners, may reduce potential worker exposures from cotton harvest. However, 1) EPA is limited to the conventional harvest TC exposure data and 2) the EPA assessment is protective for cotton harvest workers using the conventional harvest equipment (i.e., EPA cannot assume that all cotton harvest is conducted with either conventional harvest practice equipment employing new technologies, or conducted with the newer mini-module harvester).

Additional Information on Mechanical Cotton Harvest Transfer Coefficients (National Cotton Council)
NCC appreciated HED's recognition of their 2016 Survey of Harvest Transport Practices and committed to work with the EPA to develop appropriate pathways related to harvest and post-harvest practices associated with current production. The NCC included additional information relating to cotton trailer packing, conventional module builders, the harvesters with round bale module, and the harvester with mini-module.

EPA Response: EPA appreciates the additional information relating to cotton harvest practice and encourages further engagement with the NCC to better understand and evaluate cotton harvest exposures and risk.

[3] Steve Hensley. Response: Docket ID Number EPA-HQ-OPP-2012-0167. 04/30/2018.

Dislodgeable Foliar Residue Data Requirement (National Cotton Council)
The NCC is not in agreement with entry and exposure assumptions regarding Dislodgeable Foliar Residue (DFR) and Dislodgeable Boll Residue (DBR). Crop production equipment today has greatly advanced beyond practices utilized at the period of time these exposure pathways were developed (eg. DBR in the early 1990's). The NCC desires further engagement with EPA to appropriately revise these exposure pathways to reflect today's technology."..." Additionally, the NCC does not believe DFR and DBR assumptions of contact are appropriate. When paraquat is used as a defoliant, the crop is ready for harvest. Pest scouting by individuals has ended.

EPA Response: The paraquat HHRA recommends for dislodgeable foliar residue (DFR) and dislodgeable boll residue (DBR) data for paraquat. While data needs are identified for both, EPA encourages prioritization of the DBR data. As described in a prior response, EPA is limited to use of the best available data, a conventional harvest TC study which is not reflective of newer technologies such as closed cab filtered air conditioners; therefore, the occupational post-application risks presented are not reflective of newer technologies but assume that the older conventional practice harvest technologies remain in practice and are protective for harvest workers using this equipment. Further, the agency evaluated available field trial data for paraquat residues on desiccated commodities. Residues were detectable in undelinted cotton seed up to 14 day PHI and cotton gin byproducts at 3 day PHI. Field trial data are not typically used for quantitative assessment of occupational post-application exposures and risks since these data represent residues available in/on the plant and, therefore, potentially overestimate the foliar residues to which a worker would be exposed. However, these data confirm the presence of paraquat residues in cotton bolls and were considered relevant for qualitative characterization of potential occupational post-application exposures. In the absence of DBR data for cotton, EPA uses default inputs to estimate this value for risk assessment. The submission of paraquat DBR data would allow for a refined assessment of potential occupational post-application exposures from cotton harvest activities.

Occupational Post-application Exposure Estimates Are Not Reflective of Current Technology in Cotton Production (USDA)

EPA Response: The HHRA extensively discusses the occupational post-application assessment including the cotton harvest equipment types assumed and the exposure data (TCs) used. Further, the risk assessment details the use of 2016 survey data submitted by the National Cotton Council and uses these data to develop characterization for the mechanical harvest equipment type and harvest activities assessed. As described in a previous comment, the agency acknowledges that the survey information, "suggests that technology is moving increasingly toward the newer mini-module harvesters, the conventional harvest practice remains in use by approximately half of the study participants," and that these new technologies, "may reduce potential worker exposures from cotton harvest." However, the occupational post-application assessment was conducted with the intent to be protective for all potential equipment types and associated harvest activities.

EPA Occupational Handler Inputs and Assumptions (USDA)
For occupational handler exposure scenarios of concern, USDA urges EPA to consider the most up-to-date and realistic estimates for typical application rates, modern application equipment technology, and typical agricultural practices when addressing these risks within the context of paraquat's high importance to agriculture. For example, USDA notes that flagging is no longer a common practice for aerial application.

EPA Response: Per HED policy, the occupational handler risk assessment relies on maximum registered application rates. This approach ensures a health protective assessment for the potential handling of paraquat at allowable application rates. The agency may consider the assessment of typical use rates as a risk mitigation option; i.e., reducing the maximum application rates allowed by product labeling.

At the time of EPA's HHRA, the most up-to-date exposure data were used to conduct the occupational handler exposure scenarios assessed. In March 2020, EPA made public and updated the reference table which captures changes to the unit exposures recommended for occupational handler assessment. The occupational handler assessment will be updated, where changes are applicable. The update encompasses the best exposure data available to EPA and are intended to be representative of modern application equipment and typical agricultural practice.

EPA Fails to Account for the Actual Use Pattern of Alfalfa (USDA)
In general, paraquat is most commonly applied to alfalfa as a burn-down tool post-planting and pre-emergence. In some cases, paraquat can be applied between cuttings to provide a burn-down benefit, similar to what is done by flaming. Paraquat would never be applied to fully grown alfalfa fields, from which EPA's exposure estimates are derived.

EPA Response: As described in the HHRA, the agency consulted with OPP's Biological and Economic Analysis Division (BEAD) relating to the occupational post-application activities associated with the registered uses of paraquat. Broadcast applications of paraquat are applied directly to the crop for foliage desiccation (to the crop and any weeds in the field) to expedite harvest and reduce seed loss upon harvest. Per BEAD, at this late stage of the crops, scouting to make sure the application was effective, would be the only activity conducted. Further, per BEAD, the EPA Special Local Need (SLN) product registration, Paraquat SL Herbicide (EPA Reg. No. 82557-1), allows for applications immediately prior to alfalfa harvest. The agency assessed scouting for alfalfa in accordance with this recommendation. The agency will consult further with BEAD and consider the additional information provided by USDA as characterization relating to scouting activities in alfalfa.

USDA Suggests the Default 48-Hour Re-Entry Interval (REI) Negatively Impacts Growers and Is Highly Unlikely to Exist Under Real World Conditions (USDA)

EPA Response: Under 40 CFR 156.208, Subpart K. Worker Protection Statements, (c) (2), active ingredients classified as Acute I for acute dermal, eye irritation and primary skin irritation are assigned a 48-hour REI. Therefore, for paraquat, a Toxicity Category I eye irritant, a minimum 48-hour REI is required.

EPA Only Assesses Broadcast Applications (Pesticide Action Network)
There is no acknowledgement of occupational exposure except for the broadcast application route. For directed applications the assumption is that occupational post application exposures are not likely; which seems an overly risky assumption considering the high toxicity of paraquat.

EPA Response: For occupational handler risk assessment, the agency assessed all application types including both broadcast and directed. For occupational post-application risk assessment, the application type (broadcast or directed) was taken into account when determining the likelihood of foliar contact by workers performing activities following paraquat applications. The agency assumed that directed spray applications of paraquat are targeted for control of individual weeds and grasses. Such applications are made with the intent of minimizing the risk of injuring the crop and/or non-target vegetation which are not tolerant of directed applications. Since these applications are not expected to result in foliar residues on the crop and/or non-target vegetation, occupational post-application exposures are not likely for directed applications and were not assessed. Occupational post-application risks from broadcasted applications were assessed due to the likelihood of residues on foliar surfaces and worker contact while conducting activities.

Proposed Label Amendments to Address Estimated Spray Drift Risks (Syngenta Crop Protection)
Syngenta is submitting a label amendment for Gramoxone 3LB (EPA Reg. No. 100-1652) and will be modifying the pending registration label for Gramoxone Magnum (EPA Reg. No. 100-RAUR) to add the following use restrictions for applications:
• Applicators are required to use a coarse or larger spray quality (droplet size) according to the American Society of Agricultural and Biological Engineers (ASABE) Standard S572.2 for spray applications.
• Requiring that ground applications NOT exceed a boom height of 24 inches above target pest or crop canopy.
When these changes are factored into the AgDrift exposure estimates for the nonoccupational spray drift scenarios, the resulting MOEs (combined dermal and incidental oral risk estimates from indirect exposure to paraquat upon modelled deposition at 0 feet from the field's edge) were determined to be ≥ 115 which is above the minimum required LOC (MOE ≥ 100) for all populations.

EPA Response: The agency will consider Syngenta's label amendment proposal for mitigation of spray drift risks during Registration Review.

Occupational Mixer Loader Risk Assessment: Paraquat Closed System Transfer (Syngenta Crop Protection)
Syngenta has developed a closed transfer system that complies with the paraquat human health mitigation decision (HHMD) requirements being implemented for paraquat products distributed in containers < 120 gallons. In addition to minimizing the potential for exposure to the mixer/loader during the dispensing by ensuring integrity of the closed system throughout the process, this system also functions to rinse the container with pressurized water to remove any residual product in the container.

EPA Response: HED acknowledges Syngenta's development of the closed system technology being implemented for products distributed in containers < 120 gallons. The agency's occupational handler assessment for mixing/loading paraquat with a closed system is based on the best exposure data currently available for closed system technologies; the estimated risks are assumed to be the best representation of the potential exposures from this handling activity. New exposure data for closed loading of liquid formulations conducted by the Agricultural Handler Exposure Task Force is under review by the agency. These data will be used to update the paraquat handler assessment for this exposure scenario when the agency's review is finalized and these data are approved and incorporated for use.

Paraquat Mandated Label PPE (Syngenta Crop Protection)
For some products, instead of using increased PPE, an engineering-controlled (closed system) solution is used which may allow for a reduction in PPE due to the protective nature of the enclosed system. For paraquat products, the mandated transition to closed Public Comments Syngenta Crop Protection, LLC Docket: EPA–HQ–OPP–2011–0855 December 16, 2019 Page 16 systems does not include a reduction in the extensive PPE mandated by the current labels.

EPA Response: The agency occupational handler assessment intentionally presented risks to all levels of personal protection, as well as the closed system, to account for occupational handler exposure scenarios and associated risks which do not fall under the mandated transition to closed system; i.e., bulk containers greater than 120 gallons or mixing/loading/applying exposure scenarios for which a closed system is not a feasible option.

The Dislodging of Paraquat Residues from Plants (Syngenta Crop Protection)
The physico-chemical properties of paraquat result in rapid foliar adsorption and any remaining surface residues would strongly adhere to plant surfaces. The dislodging of these residues would be minimal under the mild conditions utilized in DFR studies. In the absence of DFR/DBR data for paraquat, the

Agency has utilized field crop trial residue data for qualitative characterization of paraquat post application exposure risks.

EPA Response: In the absence of DFR or DBR exposure data, HED policy is to rely on a default transfer value of 25% from foliar surfaces. While this value may overestimate residues transferring from foliar surfaces following paraquat application, the agency has no other data from which to rely to refine this estimate. Therefore, DFR/DBR data were recommended to refine the occupational post-application risk estimates.

Alfalfa Maximum Application Rate (Syngenta Crop Protection)
The agency's risk calculations were based upon a single maximum application rate for alfalfa of 1.5 lb paraquat cation/Acre. This application rate is higher than the maximum allowed single application rate for alfalfa on Syngenta paraquat products which is 1.0 lb paraquat cation/Acre.

EPA Response: For the purpose of occupational risk assessment, HED uses the maximum application rate for all crops in consideration of all products and pesticide registrants. While the Syngenta product is registered for alfalfa use at a maximum application rate of 1.0 lb cation/A, the special local need (SLN) registrations CO170001 and WY140004 associated with product EPA Reg. No. 66222-130 allow for a maximum application rate of 1.5 lb cation/A.

Changes in Cotton Harvest Technologies (Syngenta Crop Protection)
While the Agency has acknowledged cotton harvest practice is moving to these new mechanized approaches, the risk assessments for post-application harvest activities in the draft risk assessments were driven by the older higher exposure manual practices that despite becoming obsolete, were still assessed.

EPA Response: As described in the responses to the National Cotton Council public comments, "EPA's assessment of occupational post-application exposures and risks from cotton harvesting are based on transfer coefficient (TC) data derived from a study which measured exposures resulting from conventional harvest practice and associated activities. The paraquat occupational post-application assessment also considered the submission of summary information from a 2016 survey by the National Cotton Council[4] and an October 18, 2018 meeting with OPP and the National Cotton Council. While this information suggests that technology is moving increasingly toward the newer mini-module harvesters, the conventional harvest practice remains in use by approximately half of the study participants. EPA acknowledges that the newer mini-module harvester, as well as new technologies such as closed cab filtered air conditioners, may reduce potential worker exposures from cotton harvest. However, 1) EPA is limited to the conventional harvest TC exposure data and 2) the EPA assessment is protective for cotton harvest workers using the conventional harvest equipment (i.e., EPA cannot assume that all cotton harvest is conducted with either conventional harvest practice equipment employing new technologies, or conducted with the newer mini-module harvester)."

Human Flagger Assessment Is Not Practical (Syngenta Crop Protection)
From a practical standpoint, the use of human flaggers for aerial applications is exceptionally low and as referenced in Agency's assessment was determined by National Agricultural Aviation Association (NAAA) to have fallen to 1% in 2012. In the pending label amendment for Gramoxone 3Lb, the use of human flaggers for aerial applications of paraquat will be prohibited.

EPA Response: Per the paraquat HHRA, "The Agency matches quantitative occupational exposure assessment with appropriate characterization of exposure potential. While the agency presents

[4] Steve Hensley. Response: Docket ID Number EPA-HQ-OPP-2012-0167. 04/30/2018.

quantitative risk estimates for human flaggers where appropriate, agricultural aviation has changed dramatically over the past two decades. According to the 2012 National Agricultural Aviation Association (NAAA) survey of their membership, the use of GPS for swath guidance in agricultural aviation has grown steadily from the mid 1990's. Over the same time period, the use of human flaggers for aerial pesticide applications has decreased steadily from ~15% in the late 1990's to only 1% in the most recent (2012) NAAA survey. The Agency will continue to monitor all available information sources to best assess and characterize the exposure potential for human flaggers in agricultural aerial applications."

Enclosed Airplane Cockpit Exposures (Syngenta Crop Protection)
The use of enclosed cockpits and cabs for applicators reduces the potential for exposure to application sprays and for a low volatility product like paraquat, there would be no potential for exposure to vapours. Furthermore, requiring a pilot operating in an enclosed cockpit to wear a respirator may interfere with the safe operation of the aircraft.

EPA Response: Per the paraquat HHRA, "HED has no data to assess exposures to pilots using open cockpits. The only data available is for exposure to pilots in enclosed cockpits. Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks); per the Agency's Worker Protection Standard stipulations for engineering controls, pilots are not required to wear protective gloves for the duration of the application." The HHRA did not quantify exposures to pilots wearing a respirator as a risk mitigation option.

VI. Tolerances and Residue Chemistry

Table 2.2.2 Contains Several Discrepancies that Require Clarification (Washington State Department of Agriculture)

The Washington State Department of Agriculture (WSDA) identified several discrepancies and misprints in Table 2.2.2 of the HHRA. The agency provides the following corrections and clarifications in response to their comments pertaining to the tolerances (in italics):

1) *In Table 2.2.2. Summary of Paraquat Established and Recommended Tolerances for Registration Review, the following seem inconsistent: Cotton, gin byproducts—the established tolerance was 110.0, the revised tolerance is 100, and the reason is "Corrected value to be consistent with OECD Rounding Class." Shouldn't the revised value be 110 (instead of 100) to be consistent with the OECD Rounding Class? The assumption is made that the tolerances are listed in parts per million (ppm) but this is not clearly stated. Are the tolerances listed supposed to be ppm? Endive—the established tolerance was 0.05, the revised tolerance is 0.07, but there is no explanation of this change in the comments field.*

   EPA Response: The correct cotton gin byproducts tolerance is 150 parts-per-million (ppm) following Organisation for Economic Co-operation and Development (OECD) Maximum Residue Level (MRL) Calculator input. There will be a listing for ppm added to columns for tolerance value. The endive tolerance will remain at 0.05 ppm.

2) *In Table 2.2.2. Summary of Paraquat Established and Recommended Tolerances for Registration Review, the following seem inconsistent: Spanish lime-- the established tolerance was 0.05, but there is no revised tolerance, and no comment. Has the tolerance for this commodity been revoked or has it been combined into another commodity group? Sugar apple-- the established tolerance was 0.05, but there is no revised tolerance, and no comment. Has the tolerance for this commodity been revoked or has it been combined into another commodity group?*

EPA Response: There are no changes to the established tolerances for Spanish lime and sugar apple. A comment will be added to the table explaining the revised tolerances are identical to the established tolerances.

3) *In Table 2.2.2. Summary of Paraquat Established and Recommended Tolerances for Registration Review, the following seems inconsistent: Wheat, forage-- the established tolerance was 0.5, the revised tolerance is 0.5. There does not appear to be a change, however "Corrected value to be consistent with OECD Rounding Class" is stated in the comments field. Is there supposed to be a different value?*

EPA Response: The comment "Corrected value to be consistent with OECD Rounding Class" was provided erroneously for the wheat, forage tolerance and will be removed.

The EPA Should Require Analytical Standards for Enforcement (Beyond Pesticides)
Analytical standards for paraquat need to be submitted because an enforcement analytical method is required.

EPA Response: The agency identified this as a deficiency in the HHRA and Syngenta has committed to submitting the standards in their comment.

VII. General Editorial Comments (Washington State Department of Agriculture)

Paraquat dichloride is incorrectly identified as an insecticide. It is an herbicide.

EPA Response: The agency thanks the WSDA for their comment and will correct this error.

VIII. References

1. Allen MT and Levy LS. 2013. Parkinson's disease and pesticide exposure – a new assessment. *Crit Rev Toxicol*. 43(6): 515-534, DOI: 10.3109/10408444.2013.798719

2. Bartek MJ, Labudde JA, and Maibach HI. 1972. Skin permeability *in vivo*: Comparison in rat, rabbit, pig and man. *J Invest Dermatol*. 58(3):114-123.

3. Blondell J. 08/10/2000. D260797. Review of Paraquat Incidents Reports Involving Inhalation.

4. Breckenridge CB, Berry C, Chang ET, Jr RLS, and Mandel JS. 2016. Association between Parkinson's Disease and Cigarette Smoking, Rural Living, Well-Water Consumption, Farming and Pesticide Use: Systematic Review and Meta-Analysis. *PLOS ONE* 11:e0151841. doi:10.1371/journal.pone.0151841.

5. Britton W, Morton T, and Wray A. 06/26/2019. D430827. Paraquat Dichloride: Draft Human Health Risk Assessment in Support of Registration Review.

6. Brouwer M, Huss A, van der Mark M, Nijssen PCG, Mulleners WM, Sas AMG, van Laar T, de Snoo GR, Kromhout H, Vermeulen RCH. 2017. Environmental exposure to pesticides and the risk of Parkinson's disease in the Netherlands. *Environ Int*. 107:100-110.

7. Caballero M, Amiri S, Denney JT, Monsivais P, Hystad P, and Amram O. 2018. Estimated residential exposure to agricultural chemicals and premature mortality by Parkinson's disease in Washington state. *Int J Environ Res Public Health*. 15(12): 2885. doi: 10.3390/ijerph15122885.

8. Chinta SJ, Woods G, Demaria M, Rane A, Zou Y, McQuade A, Rajagopalan S, Limbad C, Madden DT, Campisi J, and Andersen JK. 2018. Cellular senescence is induced by the environmental neurotoxin paraquat and contributes to neuropathology linked to Parkinson's disease. *Cell Rep*. 22(4): 930-940.

9. Costello S, Cockburn M, Bronstein J, Zhang X, and Ritz B. 2009. Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California. *Am J Epidemiol*. 169(8):919-926.

10. Elbaz A, Clavel J, Rathouz PJ, Moisan F, Galanaud JP, Delemotte B, Alpérovitch A, and Tzourio C. 2009. Professional exposure to pesticides and Parkinson disease. *Ann Neurol*. 66(4):494–504.

11. Evans E and Recore S. D446902. 07/25/2018. Paraquat: Tier II Human Incidents Report.

12. Feldman RJ and Maibach HI. 1966. Percutaneous penetration of 14C hydrocortisone in man. II. Effect of certain bases and pretreatments. *Arch Dermatol*. 94(5): 649-651.

13. Firestone JA, Lundin JI, Powers KM, Smith-Weller T, Franklin GM, Swanson PD, Longstreth WT, and Checkoway H. 2010. Occupational Factors and Risk of Parkinson's Disease: A Population-Based Case-Control Study. *Am J Ind Med*. 53:217-223.

14. Firestone JA, Smith-Weller T, Franklin G, Swanson P, Longstreth, Jr WT, and Checkoway H. 2005. Pesticides and risk of Parkinson disease; A population-based case-controls study. *Arch Neurol*. 62:91-95.

15. Freire C and Koifman S. 2012. Pesticide exposure and Parkinson's disease: Epidemiological evidence of association. *Neurotoxicol*. 33:947–71. doi:10.1016/j.neuro.2012.05.011.

16. Kuopio AM, Marttila RJ, Helenius H, and Rinne UK. 1999. Environmental risk factors in Parkinson's disease. *Mov Disord*. 14(6):928–39.

17. Liou HH, Tsai MC, Chen CJ, Jeng JS, Chang YC, Chen SY, and Chen RC. 1997. Environmental risk factors and Parkinson's disease: A case-control study in Taiwan. *Neurol*. 48:1583-1588.

18. Marks L. 2007a. Investigating reported paraquat-induced neurotoxicity in the Alderley Park C57 black mouse: The neurochemical and pathological effects on the dopaminergic system of 3 weekly injections of 10 mg/kg 1,1'dimethyl-4,4'-bipyridinium (Paraquat). *Unpublished*.

19. Marks L. 2007b. Investigating reported paraquat-induced neurotoxicity in the Charles River C57 black mouse: The neurochemical and pathological effects on the dopaminergic system of 3 weekly injections of 1,1'dimethyl-4,4'-bipyridinium (Paraquat). *Unpublished*.

20. Marks L. 2007c. Investigating reported paraquat-induced dopaminergic neurotoxicity in the Charles River C57 black mouse: The neurochemical, neuropathological and neurobehavioural effects of increasing the dosing frequency of 1,1'dimethyl-4,4'-bipyridinium (Paraquat). *Unpublished*.

21. Morton T, Khasawinah A, Assaad A, and Miller JS. D415809. 09/25/2014. Paraquat Dichloride. HED Human Health Risk Assessment for the Expansion of Representative Commodity Use on Potato to Tuberous and Corm Vegetables Subgroup 1C.

22. Niman A. 06/26/2019. D449108. Paraquat Dichloride: Tier II Epidemiology Report.

23. Phillips L, Steinberg M, Maibach HI, and Akers WA. 1972. A comparison of rabbit and human skin response to certain irritants. *Tox Appl Pharmacol*. 21(3):369-382.

24. Ray WJ. 2011. Analysis of brain samples from paraquat-exposed squirrel monkeys for residues of paraquat. *Unpublished*.

25. Rugbjerg K, Harris MA, Shen H, Marion SA, Tsui JK, and Teschke K. 2011. Pesticide exposure and risk of Parkinson's disease—a population-based case-control study evaluating the potential for recall bias. *Scand J Work Environ Health*. 37(5):427–36.

26. Scott R, Walker M, and Dugard PH. 1986. A comparison of the in vitro permeability properties of human and some laboratory animal skins. *Int J Cosmetic Sci*. 8(4):189-194.

27. Seidler A, Hellenbrand W, Robra BP, Vieregge P, Nischan P, Joerg J, Oertel WH, Ulm G, and Schneider E. 1996. Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. *Neurology*. 46(5):1275–84.

28. Semchuk K, Love EJ, and Lee RG. 1992. Parkinson's disease and exposure to agricultural work and pesticide chemicals. *Neurology*. 42(7):1328–1335.

29. Shrestha S, Kamel F, Umbach DM, Fan Z, Freeman LB, Koutros S, Alavanja M, Blair A, Sandler DP, and Chen H. 2018. Factors associated with dream enacting behaviors among US farmers. *Parkinsonism Relat Disord*. 57: 9-15.

30. Tamano H, Nishio R, Morioka H, Furuhata R, Komata Y, and Takeda A. 2019. Paraquat as an environmental risk factor in Parkinson's disease accelerates age-related degeneration via rapid influx of extracellular Zn2+ into nigral dopaminergic neurons. *Mol Neurobiol*. 56(11): 7789-7799.

31. Tangamornsuksan W, Lohitnavy O, Sruamsiri R, Chaiyakunapruk N, Scholfield CN, Reisfeld B, and Lohitnavy M. 2018. Paraquat exposure and Parkinson's disease: A systematic review and meta-analysis. *Arch Environ Occup Health*. 1-14. doi: 10.1080/19338244.2018.1492894.

32. Tanner CM, Ross GW, Jewell SA, Hauser RA, Jankovic J, Factor SA, Bressman S, Deligtisch A, Marras C, Lyons KE, Bhudhikanok GS, Roucoux DF, Meng C, Abbott RD, and Langston JW. 2009. Occupation and risk of parkinsonism: a multicenter case-control study. *Arch Neurol*. 66(9): 1106-13.

33. Terron A, Bal-Price A, Paini A, Monnet-Tschudi F, Bennekou SH, EFSA WG EPI1 Members, Leist M, and Schildknecht S. 2018. An adverse outcome pathwary for parkinsonian motor deficits associated with mitochondrial complex I inhibition. *Arch Toxicol*. 92(1): 41-82.

34. Tomenson JA and Campbell C. 2011. Mortality from Parkinson's disease and other causes among a workforce manufacturing paraquat: A retrospective cohort study. *Br Med J Open*. 1-7.

35. Vaccari, C, El Dib R, Gomaa H, Lopes LC, and de Camargo JL. 2019. Paraquat and Parkinson's disease: A systematic review and meta-analysis of observational studies. *J Toxixol Environ. Health B*. 22:172–202.

36. van der Mark M, Vermeulen R, Nijssen PCG, Mulleners WM, Sas AMG, van Laar T, Brouwer M, Huss A, and Kromhout H. 2014. Occupational exposure to pesticides and endotoxin and Parkinson disease in the Netherlands.. *Occup Environ Med*. 71(11):757-764.

37. Wray A and Niman A. 06/26/2019. D449106. TXR 0057888. Paraquat Dichloride: Systematic Review of the Literature to Evaluate the Relationship Between Paraquat Dichloride Exposure and Parkinson's Disease.

38. Wray A. 06/26/2019. D449107. TXR 0057887. Paraquat Dichloride: Review of the Paraquat Dichloride Open Literature for Registration Review.

39. Tieu K. 2011. A guide to neurotoxic animal models of Parkinson's disease. Cold Spring Harb Perspect Med. 1(1): a009316.

40. McDowell K and Chesselet MF. 2012. Animal models of the non-motor features of Parkinson's disease. *Neurobiol Dis.* 46(3): 597-606.

41. Colle D, Farina M, Ceccatelli S, Raciti M. 2018. Paraquat and Maneb Exposure Alters Rat Neural Stem Cell Proliferation by Inducing Oxidative Stress: New Insights on Pesticide-Induced Neurodevelopmental Toxicity. *Neurotox Res.* 34(4):820-833.

42. Rury, K. 04/12/2012. Paraquat: Summary of Hazard and Science Policy Council (HASPOC) Meeting of April 12, 2012: Recommendations on the need for a developmental toxicity study in rabbits. TXR 0056294.